

METHODS USING MONOVALENT ANTIGEN BINDING CONSTRUCTS TARGETING HER2

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 15/036,175, filed May 12, 2016 (pending), which a US National Phase Application of International Application No. PCT/US2014/065571, filed Nov. 13, 2014, which claims the benefit of U.S. Provisional Application No. 61/903,839, filed Nov. 13, 2013, all of which are hereby incorporated in their entirety by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Dec. 16, 2020, is named ZWI-020C1_sequence-listing.txt, and is 355,986 bytes in size.

BACKGROUND

[0003] In the realm of therapeutic proteins, antibodies with their multivalent target binding features are excellent scaffolds for the design of drug candidates. Current marketed antibody therapeutics are bivalent monospecific antibodies optimized and selected for high affinity binding and avidity conferred by the two antibody FABs. Defucosylation or enhancement of FcγR binding by mutagenesis have been employed to render antibodies more efficacious via antibody Fc dependent cell cytotoxicity mechanisms. Afucosylated antibodies or antibodies with enhanced FcγR binding still suffer from incomplete therapeutic efficacy in clinical testing and marketed drug status has yet to be achieved for any of these antibodies.

[0004] Therapeutic antibodies would ideally possess certain minimal characteristics, including target specificity, biostability, bioavailability and biodistribution following administration to a subject patient, and sufficient target binding affinity and high target occupancy and antibody binding to target cells to maximize antibody dependent therapeutic effects. There has been limited success in efforts to generate antibody therapeutics that possess all of these minimal characteristics, especially antibodies that can fully occupy targets at a 1:1 antibody to target ratio. For example, traditional bivalent monospecific IgG antibodies cannot fully occupy targets at a 1:1 ratio even at saturating concentrations. From a theoretical perspective, at saturating concentrations a traditional monospecific bivalent antibody is expected to maximally binds targets at a ratio of 1 antibody:2 targets owing to the presence of two identical antigen binding FABs that can confer avidity effects compared to monovalent antibody fragments. Further, such traditional antibodies suffer from more limited bioavailability and/or biodistribution as a consequence of greater molecular size. Furthermore, traditional antibodies may in some cases exhibit agonistic effects upon binding to a target antigen, which is undesired in instances where the antagonistic effect is the desired therapeutic function. In some instances, this phenomenon is attributable to the “cross-linking” effect of a bivalent antibody that when bound to a cell surface receptor promotes receptor dimerization that leads to receptor activation. Additionally, traditional bivalent antibodies suffer from limited therapeutic efficacy

because of limited antibody binding to target cells at a 1:2 antibody to target antigen ratio at maximal therapeutically safe doses that permit antibody dependent cytotoxic effects or other mechanisms of therapeutic activity.

[0005] Monovalent antibodies that bind HER2 have been described in International Patent Publication Nos. WO 2008/131242 (Zymogenetics, Inc.) and WO 2011/147982 (Genmab A/S). Co-owned patent applications PCT/CA2011/001238, filed Nov. 4, 2011, PCT/CA2012/050780, filed Nov. 2, 2012, PCT/CA2013/00471, filed May 10, 2013, and PCT/CA2013/050358, filed May 8, 2013 describe therapeutic antibodies. Each is hereby incorporated by reference in their entirety for all purposes.

SUMMARY

[0006] Disclosed herein are methods of treating a subject, e.g., a human, by administering an effective amount of a first monovalent antigen-binding construct, e.g., antibody, or a combination of a first and a second monovalent antigen-binding construct to the subject, the first and second monovalent antigen-binding constructs each having an antigen-binding polypeptide construct and a dimeric Fc coupled, with or without a linker, to the antigen-binding polypeptide construct. Each antigen-binding polypeptide construct specifically binds a extracellular domain 2 (ECD2) of human epidermal growth factor receptor 2 (HER2), a ECD4 of HER2, or a ECD1 of HER2. The first monovalent antigen-binding construct and the second monovalent antigen-binding construct bind to non-overlapping epitopes and do not compete with each other for binding to HER2.

[0007] In various embodiments, the method of treating a subject includes, for example, inhibiting growth of a HER2+ tumor, delaying progression of a HER2+ tumor, treating a HER2+ cancer or preventing a HER2+ cancer. The HER2+ tumor or cancer can be breast, ovarian, stomach, gastroesophageal junction, endometrial, salivary gland, head and neck, lung, brain, kidney, colon, colorectal, thyroid, pancreatic, prostate or bladder tumor or cancer.

[0008] In some embodiments, the monovalent antigen-binding constructs used in the methods described herein include a heterodimeric Fc comprising at least two CH3 sequences and the dimerized CH3 sequences have a melting temperature (T_m) of about 68° C. or higher. In some embodiments, the monovalent antigen-binding constructs used in the methods described herein selectively and/or specifically binds HER2 with a greater maximum binding (B_{max}) as compared to a monospecific bivalent antigen-binding construct that specifically binds HER2, and wherein at a monovalent antigen-binding construct to target ratio of 1:1 the increase in B_{max} relative to the monospecific bivalent antigen-binding construct is observed at a concentration greater than the observed equilibrium constant (K_D) of the constructs up to saturating concentrations.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIGS. 1A, B, and C depict schematic representations of different OA antibody formats. FIG. 1A depicts the structure of a bivalent mono-specific, full-sized antibody, where the light chains are shown in white, the Fab portion of the heavy chain is shown in hatched fill, and the Fc portion of the heavy chains are grey. FIG. 1B depicts two versions of a monovalent, mono-specific OA where the antigen-binding domain is in the Fab format. In both of these